

REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-13, 16-18, and 27-36 are pending in this application and are presented for examination. Claims 14-15 and 19-26 have been canceled without prejudice. Claims 1-13 and 16-18 have been withdrawn from consideration as being directed to non-elected inventions. Claims 27-36 are newly added, and are drawn to the elected invention. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

Support for new claims 27-36 is found throughout the specification as filed. A detailed description of the support for new claim 27 is provided below. Support for new claims 28-29 is found, for example, on page 10, lines 13-16. Support for new claim 30 is found, for example, on page 5, lines 4-7. Support for new claim 31 is found, for example, on page 34, lines 11-22. Support for new claim 32 is found, for example, on page 76, lines 4-6. Support for new claim 33 is found, for example, on page 31, lines 10-24. Support for new claim 34 is found, for example, on page 83, lines 15-17. Support for new claim 35 is found, for example, on page 83, lines 6-8. Support for new claim 36 is found, for example, on page 5, lines 30-33 and on page 28, lines 10-14. Thus, no new matter has been introduced. As such, Applicant respectfully requests that the new claims be entered.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 14-15 and 19-26 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter and lacking sufficient written description. In particular, the Examiner alleges that claims 14-15 and 19-26 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicant, at the time the application was filed, had possession of the claimed invention. In response, Applicant has canceled claims 14-15 and 19-26 without prejudice, thereby rendering this rejection moot. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Newly added claim 27 recites an array for diagnosing inflammatory bowel disease (IBD) in a subject comprising nucleic acid probes for determining an expression level of at least one gene product in a sample from the subject, wherein the gene product is an mRNA of a gene selected from the group consisting of macrophage inflammatory protein-2 β (GRO3), neutrophil lipocalin (HNL), elastase specific inhibitor (elafin), and type VI collagen α 3 chain (COL6A3); and a substrate to which the nucleic acid probes are bound, wherein a difference in the expression level of the gene product in the subject compared to an expression level of the gene product in a healthy subject indicates that the subject has IBD or is at risk of developing IBD.

Applicant believes that newly added claim 27 finds clear support in the specification as filed. For example, the specification discloses that the arrays of the present invention comprise nucleic acid probes for determining the expression level of at least one IBD gene product and a substrate to which the nucleic acid probes are bound (*see*, page 5, lines 28-33). The specification also discloses that the expression level of an IBD gene product is determined in a sample (*see*, page 5, lines 13-15). In particular, the sample is obtained from a subject and the expression level of the gene product (*i.e.*, the mRNA level) is determined and compared to the level of the gene product in a healthy subject (*see*, page 76, lines 19-22). A difference in the expression level of the gene product (*i.e.*, an abnormal mRNA level) indicates that the subject has IBD or is at risk of developing IBD (*see*, page 76, lines 23-25).

Table 1 describes a list of the genes identified by Applicant whose gene products display differential expression in UC or CD relative to control samples. In particular, Table 1 shows that the macrophage inflammatory protein-2 β (GRO3) gene product is overexpressed by 3.4-fold in UC relative to control samples (*see*, page 93, class I). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its GenBank accession number (X53800) into the National Center for Biotechnology Information (NCBI) online database (<http://www.ncbi.nlm.nih.gov/>). For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

Similarly, Table 1 shows that the neutrophil lipocalin (HNL) gene product is overexpressed by 35.5-fold in UC relative to control samples (*see*, page 94, class II). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its

GenBank accession number (S75256) into the NCBI online database. For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

Likewise, Table 1 shows that the elastase specific inhibitor (elafin) gene product is overexpressed by 13.3-fold in UC and 3.8-fold in CD relative to control samples (*see*, page 97, class VII). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its GenBank accession number (L10343) into the NCBI online database. For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

Finally, Table 1 shows that the type VI collagen $\alpha 3$ chain (COL6A3) gene product is overexpressed by 7.3-fold in UC relative to control samples (*see*, page 97, class VII). Table 1 also provides the nucleotide sequence of this gene product, which is obtained by entering its GenBank accession number (X52022) into the NCBI online database. For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of this gene product.

In view of the foregoing, Applicant believes that new claim 27 is adequately disclosed in the specification as filed.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 14-15 and 19-26 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In response, Applicant has canceled claims 14-15 and 19-26 without prejudice, thereby rendering this rejection moot. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

IV. REJECTION UNDER 35 U.S.C. § 102(b)

Claim 14 was rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Heller *et al.* (*Proc. Natl. Acad. Sci. USA*, 94:2150-2155 (1997)). Applicant has canceled claim 14 without prejudice, thereby rendering this rejection moot. Thus, Applicant respectfully requests that this rejection be withdrawn.

Applicant asserts that newly added claim 27 is novel over Heller *et al.* In particular, Heller *et al.* simply fails to teach or suggest an array that includes nucleic acid probes

for determining the expression level of any of the claimed genes (*i.e.*, GRO3, HNL, elafin, or COL6A3). Importantly, Heller *et al.* does not teach or suggest that these genes are differentially expressed in IBD relative to control samples. Rather, Heller *et al.* discloses the differential expression of genes from rheumatoid arthritis and IBD samples that do not correspond to any of the claimed genes. As a result, given the absence of any teaching or suggestion in Heller *et al.* that the claimed genes are differentially expressed in IBD relative to control samples, the array of Heller *et al.* would not read on the claimed array. Accordingly, each and every element as set forth in new claim 27 is not found in Heller *et al.*

V. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 14-15 and 19-26 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Heller *et al.* in view of Silverman *et al.* (U.S. Patent No. 6,331,396), Poulakkainen *et al.* (*Gastroenterology*, 114:A1064 (1998)), Prehn *et al.* (*Gastroenterology*, 114:A1064 (1998)), Dieckgraefe *et al.* (*Gastroenterology*, 114:A964-965 (1998)), Dieckgraefe (U.S. Patent No. 6,228,585), and Pallone *et al.* (*Clin. Exp. Immunol.*, 74:75-79 (1988)), and further in view of the specification. Applicant has canceled claims 14-15 and 19-26 without prejudice, thereby rendering this rejection moot. Thus, Applicant respectfully requests that this rejection be withdrawn.

Applicant asserts that newly added claim 27 is unobvious over the above references either alone or in combination. As described above, Heller *et al.* not only fails to teach or suggest an array that includes nucleic acid probes for determining the expression level of any of the claimed genes (*i.e.*, GRO3, HNL, elafin, or COL6A3), but also fails to disclose that these genes are differentially expressed in IBD relative to control samples. Similarly, none of the other references teach or suggest these inventive features of the claimed array. Rather, Silverman *et al.* discloses an array with nucleic acid probes that hybridize to interferon stimulated or repressed transcripts; Puolakkainen *et al.* discloses the differential expression of stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metalloelastase (MMP-12), and TIMP-3 in intestinal ulcerations using *in situ* hybridization and immunohistochemistry; Prehn *et al.* discloses that IL-18, IL-12, IL-10, and IL-4 protein levels as determined by an immunoassay

(i.e., ELISA) remained unchanged in cells that were treated with TNF- α ; Dieckgraefe *et al.* discloses an oligonucleotide probe array that detected changes in the expression of genes in IBD specimens, without reference to any specific genes; Dieckgraefe discloses an oligonucleotide probe array that detected changes in the expression of pancreatic stone protein (PSP), pancreatitis-associated protein (PAP), and regenerating gene homologue (REGH); and Pallone *et al.* discloses the differential expression of HLA-DR, HLA-DP, and HLA-DQ in IBD using a panel of monoclonal antibodies. As a result, given the absence of any teaching or suggestion in these references that the claimed genes are differentially expressed in IBD relative to control samples, none of these references, either alone or in combination, would read on the claimed array.

In the Office Action, the Examiner alleges that the genes listed in Table 1 of the instant specification are known to be involved in IBD (*see*, page 13 of the Office Action). In response, Applicant asserts that the Examiner has improperly characterized these genes as being known for their role in IBD. With regard to new claim 27, Applicant submits that although the specifically claimed genes were known in the art, their involvement in IBD was never appreciated. In fact, the instant specification is the first to show that GRO3, HNL, elafin, and COL6A3 are differentially expressed (i.e., overexpressed) in UC and/or CD relative to control samples. As a result, contrary to the Examiner's allegation, a skilled person in the art would not have been motivated to include any of the claimed genes on an array for diagnosing IBD because it was not appreciated that detecting these genes would lead to an improved diagnosis of IBD. Therefore, Applicant believes that new claim 27 would not be rendered obvious by the instant specification, alone or in combination with any of the above references.

VI. REJECTION UNDER 35 U.S.C. § 102(b)/103(a)

Claims 14-15 and 19-26 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* (*Gastroenterology*, 114:A964-965 (1998)). Applicant has canceled claims 14-15 and 19-26 without prejudice, thereby rendering this rejection moot. Thus, Applicant respectfully requests that this rejection be withdrawn.

Applicant asserts that newly added claim 27 is novel and unobvious over Dieckgraefe *et al.* As described above, Dieckgraefe *et al.* simply fails to teach or suggest an array that includes nucleic acid probes for determining the expression level of any of the claimed genes (*i.e.*, GRO3, HNL, elafin, or COL6A3). Importantly, Dieckgraefe *et al.* does not teach or suggest that these genes are differentially expressed in IBD relative to control samples. Rather, Dieckgraefe *et al.* discloses an oligonucleotide probe array that detected changes in the gene expression of different classes of genes in IBD specimens, without reference to any particular genes in those classes. As a result, contrary to the Examiner's allegation, the claimed array is not the same or an obvious variation of the array of Dieckgraefe *et al.* due to the fact that this reference lacks any teaching or suggestion that the claimed genes are differentially expressed in IBD relative to control samples. Even assuming *arguendo* that nucleic acid probes for the claimed genes were present on the array of Dieckgraefe *et al.*, that array would still not read on the claimed array because Dieckgraefe *et al.* fails to appreciate an array that can be used to diagnose IBD by determining the differential expression of at least one of the claimed genes. Accordingly, each and every element as set forth in new claim 27 is not found in Dieckgraefe *et al.*, and the claimed array would not be rendered obvious by this reference.

VII. REJECTION UNDER 35 U.S.C. § 102(a) or (e)/103(a)

Claims 14-15 and 19-26 were rejected under 35 U.S.C. § 102(a) or (e) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe (U.S. Patent No. 6,228,585). Applicant has canceled claims 14-15 and 19-26 without prejudice, thereby rendering this rejection moot. Thus, Applicant respectfully requests that this rejection be withdrawn.

Applicant asserts that newly added claim 27 is novel and unobvious over Dieckgraefe. As described above, Dieckgraefe simply fails to teach or suggest an array that includes nucleic acid probes for determining the expression level of any of the claimed genes (*i.e.*, GRO3, HNL, elafin, or COL6A3). Importantly, Dieckgraefe does not teach or suggest that these genes are differentially expressed in IBD relative to control samples. Rather, Dieckgraefe discloses an oligonucleotide probe array that detected changes in the expression of PSP, PAP,


and REGH. As a result, contrary to the Examiner's allegation, the claimed array is not the same or an obvious variation of the array of Dieckgraefe due to the fact that this reference lacks any teaching or suggestion that the claimed genes are differentially expressed in IBD relative to control samples. Even assuming *arguendo* that nucleic acid probes for the claimed genes were present on the array of Dieckgraefe, that array would still not read on the claimed array because Dieckgraefe fails to appreciate an array that can be used to diagnose IBD by determining the differential expression of at least one of the claimed genes. Accordingly, each and every element as set forth in new claim 27 is not found in Dieckgraefe, and the claimed array would not be rendered obvious by this reference.

VIII. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

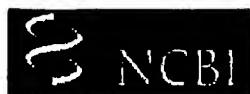
If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
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Nucleotide

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Links

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TITLE	Cloning and characterization of cDNAs for murine macrophage inflammatory protein 2 and its human homologues				
JOURNAL	J. Exp. Med. 172 (3), 911-919 (1990)				
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AUTHORS	Tekamp-Olson,P.A.				
TITLE	Direct Submission				
JOURNAL	Submitted (11-JUL-1990) Tekamp-Olson P.A., Chiron Corporation, 4560 Horton St., Emeryville, CA 94608, USA				
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AUTHORS        Bartsch,S. and Tschesche,H.
TITLE          Cloning and expression of human neutrophil lipocalin cDNA derived
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JOURNAL        FEBS Lett. 357 (3), 255-259 (1995)
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 AUTHORS Sallenave, J.M. and Silva, A.
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